# The effect of neurodegenerative diseases on the subventricular zone

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Abstract | During brain development, one of the most important structures is the subventricular zone (SVZ), from which most neurons are generated. In adulthood the SVZ maintains a pool of progenitor cells that continuously replace neurons in the olfactory bulb. Neurodegenerative diseases induce a substantial upregulation or downregulation of SVZ progenitor cell proliferation, depending on the type of disorder. Far from being a dormant layer, the SVZ responds to neurodegenerative disease in a way that makes it a potential target for therapeutic intervention.

Ganglionic eminence
An embryonic cluster of nerve cells near the ventricle, where neurons are generated before they migrate to different parts of the brain.

Progenitor cell
A dividing cell that has the capacity to differentiate.

Basal ganglion
A type of specialized nerve cell cluster that is found deep within each cerebral hemisphere and the upper brainstem. Basal ganglia consist of the caudate nucleus, the putamen, the globus pallidus, the sub-thalamic nucleus and the substantia nigra. The basal ganglia assist in initiating movement and in motor control.

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*Maurice A. Curtis and Richard L. M. Faull would like to dedicate this manuscript to their revered colleague and friend Peter S. Eriksson, M.D., Ph.D. (1959–2007).*

The subventricular zone (SVZ) contains stem cells in the regions of the medial and lateral ganglionic eminences. During brain development, these stem cells give rise to proliferative progenitor cells which then migrate from their birthplace to the cortex or the basal ganglia, where they differentiate into neurons[1–6]. In the adult brain, key characteristics of the developmental SVZ are maintained; in particular, the continuous generation of migrating neuroblasts that are destined for the olfactory bulb or for other areas of cell death in the brain[7–9]. Interestingly, studies in various animal disease models have convincingly shown that the SVZ can respond to insults in the adult brain by producing new progenitor cells that can migrate to sites that have been affected by neurodegenerative pathology or brain injury[7,10–12].

In response to neurodegeneration in Huntington's disease (HD), epilepsy and stroke, there is an upregulation of progenitor cell production, cytokine levels and migratory proteins in the SVZ, leading to an increase in the number of adult-born neurons. By contrast, in Alzheimer's disease (AD) and Parkinson's disease (PD) there are fewer proliferating cells in the SVZ. Since the discovery of neurogenesis in the adult human hippocampus in 1998 (REF. 13), the possibility has been raised that endogenous progenitor cells, the precursors of new neurons in the adult brain, might be harnessed and manipulated to provide neuronal replacement therapy. Given that the SVZ is the major source of proliferative cells in the adult brain, it is important to examine how the SVZ responds to different pathological conditions (such as HD, PD and AD, and also epilepsy, in which the neurodegenerative aspect is less clear-cut). The focus of this Review will be on the alterations that occur in the SVZ in response to neurodegeneration in humans and in animal disease models. We highlight potential therapeutic approaches that might in future be used to upregulate the production of progenitor cells and neurogenesis in the SVZ.

## The structure of the SVZ in the normal brain

The human and rodent SVZ is a region that lies immediately beneath the ependymal layer on the lateral wall of the lateral ventricles; thus, it is a niche region that is in close proximity to the nutrients and growth factors that are present in the cerebrospinal fluid (CSF) of the ventricles[9,14–16] (FIG. 1a). In the human brain, the SVZ is separated from the caudate nucleus by a layer of myelin[17], whereas in the rodent brain there is no myelin layer bordering the SVZ.

Analogous to the rodent SVZ, the adult human SVZ harbours three major cell types (A, B and C) that are differentially distributed in three layers[17–20] (FIG. 1b). Type A cells are present in small numbers in the cell-poor layer (layer 2) that lies immediately beneath the ependymal cells; in rodents, the type A cells are neuroblasts that are destined for the olfactory bulb[18,21] (BOX 1). Layer 3 is comprised of type B cells (B1 and B2 subtypes, which have different nuclear morphology; B2 cells have fewer free ribosomes and more clumped chromatin than B1 cells), which are glial fibrillary acidic protein (GFAP)-positive glial cells that form an astrocytic ribbon in the human brain. Type B cells form a well-delineated and conspicuous layer in the SVZ, between the superficial, cell-poor layer 2 and the deeper layer 4 (which consists

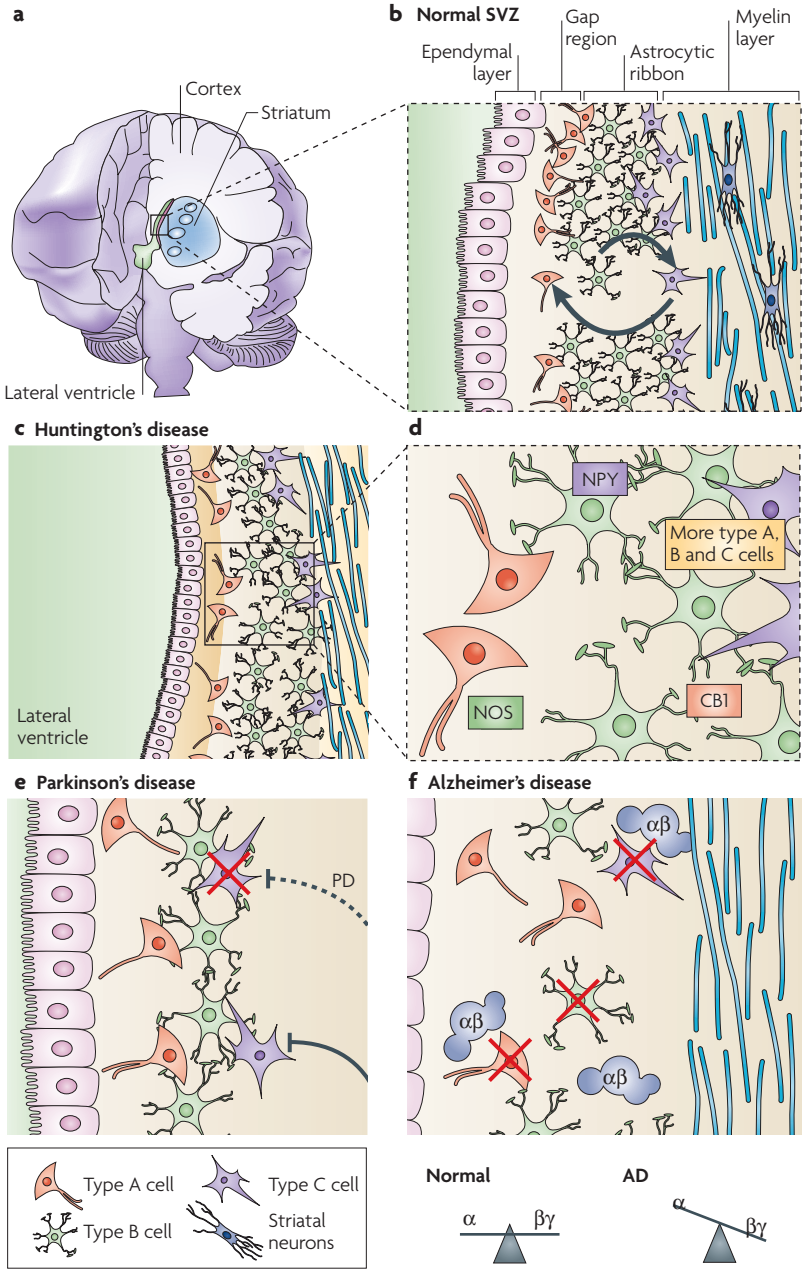



Figure 1 | **Representations of the subventricular zone (SVZ) in the normal brain and of the changes that occur in neurodegenerative disorders. a** | The SVZ is located in the wall of the lateral ventricle. It consists of an ependymal layer, a gap region and an astrocytic ribbon, and is seperated from the caudate nucleus and the striatum by a layer of myelin. **b** | The SVZ contains three different cell types (types A, B and C) that are organized in a specific pattern, with the type A cells closest to the ependymal layer, the type B cells forming the astrocytic ribbon and the type C cells located close to the myelin layer and the striatum. Arrows represent interconversion of cell types. **c** | The brain of an individual with Huntington's disease is characterized by striatal cell loss, but increased SVZ thickness. The SVZ has more type A, B and C cells than normal and is enriched in endogenous mitogenic factors, such as neuropeptide Y (NPY), nitric oxide synthase (NOS), certain GABA receptor subunits and the cannabinoid receptor CB1 (**d**). **e** | In the SVZ of individuals with Parkinson's disease (PD) there is a reduction in the dopaminergic input from the substantia nigra (depicted as a dashed inhibitory connection) that leads to the death of D2 and D3 receptor-rich type C cells (shown as red cross). The PD-affected SVZ has fewer progenitor cells. **f** | In the SVZ of individuals with Alzheimer's disease, there is a reduction in neurogenesis because there is an imbalance in the ratio of α and β/γ secretases, leading to abnormal accumulation of β-amyloid and generic cell death in the SVZ.

of myelinated fibres). In the rodent brain, type B cells are the primary progenitors of new neurons[22,23]. Type C cells (also known as transit-amplifying cells) are less numerous, and are located deep in layer 3 (very close to the myelin in layer 4). For further detail on normal SVZ anatomy, see REFS 17–19. The ratio of type A:B:C cells in the mouse brain is 3:2:1, whereas the ratio in the normal human SVZ is 1:3:1 (REFS 17,18,21).

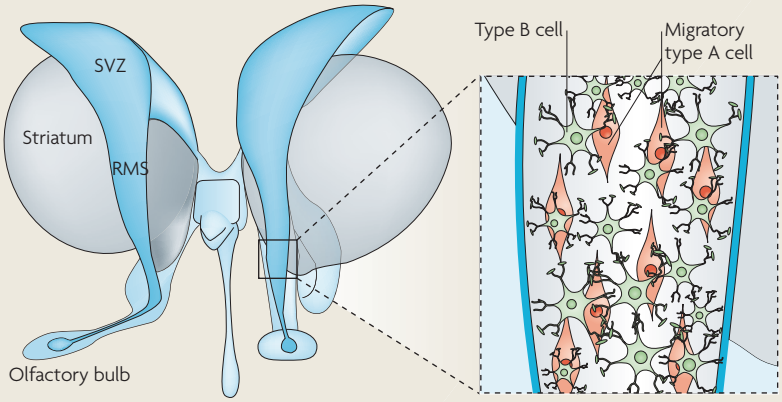
## The SVZ in neurodegenerative diseases

In HD, PD and AD, a clear neurodegeneration in a specific brain region takes place over a long period of time and, thus, the long-term response of the SVZ to the degenerative changes can be determined. By contrast, in stroke patients the pathology causes indiscriminate necrosis in the region adjacent to a blocked cerebral blood vessel, and neurodegeneration is secondary to the primary pathology (BOX 2). Likewise, in the case of epilepsy, the principal pathology does not affect regions near the SVZ (BOX 3). Although changes in the SVZ have been reported after stroke and in epilepsy, here we focus on the changes that occur in the SVZ in response to neurodegenerative disease.

***Huntington's disease.*** HD is an autosomal dominant neurodegenerative disorder that results in progressive cell death in the caudate nucleus and the putamen (collectively known as the striatum) (FIG. 1c). It is caused by an expanded CAG repeat in the huntingtin (*HD*) gene, which lies on the short arm of chromosome 4 (REFS 24–26). The striatal neuropathology in HD is graded on an ascending scale from 0 to 4 (REF. 27). A HD grade 0 brain has a grossly normal, convex caudate nucleus, but microscopically there is already a loss of projection neurons. At grade 4, the caudate nucleus is markedly concave and there is a 95% loss of projection neurons from the caudate nucleus[27,28].

In animal models of HD, the basic requirement for increased progenitor cell production in the SVZ appears to be striatal cell death. In transgenic mouse models of HD (in which there is minimal cell loss in the striatum), the SVZ is essentially unaltered[29,30]; however, in rat striatal-lesion models of HD there is a marked increase in SVZ progenitor cell proliferation and neurogenesis[31,32] (BOX 4). Furthermore, in an excitotoxic striatal lesion model of HD that was induced by quinolinic acid (QA), it was demonstrated that progenitor cells not only proliferate, but also migrate from the SVZ towards the site of the lesion, where a subgroup then differentiate into doublecortin immunoreactive, immature neurons[32]. A time course study revealed that progenitor cell proliferation had begun by day 1 following the QA lesion, that it increased to a maximum at day 7, and that it then declined to a lower, but still increased, level of proliferation at day 28 (REF. 32). Furthermore, in these same studies, neuroblasts were found to migrate away from the SVZ and into the QA lesion. Most of these neuroblasts were located in the periphery of the lesion, but a few were also detected in the core[32]. These findings demonstrate that cell death in the striatum is a powerful stimulant of progenitor cell proliferation, neuroblast migration and neurogenesis in the SVZ.

Box 1 | **The rostral migratory system (RMS) in rodents and humans**




Once development in the rodent brain has been completed, the main role of the subventricular zone (SVZ) is to provide cells for cell replacement in the olfactory bulb (OB) through the rostral migratory stream (RMS)[20,113,124]. The rodent olfactory bulb has a very high turnover of cells in the granule cell layer and the periglomerular layer, where there is a replacement of 30 granule cells to each periglomerular neuron[125]. Recently, a system by which cells that arise in the SVZ can migrate towards the olfactory bulb for neuronal replacement has been discovered in the human brain[126]. This has been termed the ventriculo-olfactory neurogenic system. The relative inactivity of the human SVZ in comparison with the rodent SVZ probably reflects the fact that the demand for cellular replacement in the human OB is much lower (because the olfactory sense is not as developed as in rodents). There are significantly more type A neuroblasts in the rodent SVZ than in the human SVZ[18,126]. Furthermore, the human OB makes up approximately 0.064% of the total human brain weight, whereas the rodent OB makes up approximately 20% of the total rodent brain weight. Interestingly, olfactory bulbectomy does not stop the production of progenitor cells in the SVZ, nor their migration, but the cells are more likely to differentiate into calretinin-positive neurons and integrate into neighbouring brain parenchyma[127,128]. Because progenitor cells move towards their target destination from the SVZ and integrate early, then they might equally be directed by appropriate migration cues towards a site of injury (for example, the striatum in Huntington's disease or the cortex in Alzheimer's disease), where they could differentiate into replacement neurons[7,32].

Neuroblast
A dividing neuronal precursor cell.

Striatum
The area of the brain that controls movement and balance. It consists of the caudate nucleus and the putamen, and it is connected to and receives signals from the substantia nigra and the cortex.

Rota-rod performance
A motor test that determines the ability of rodents to keep their balance on a rotating cylinder.

Neurosphere culture
A free-floating multidimensional cell structure that is derived from neural stem cells *in vitro*. Neurosphere assays enable the investigation of the differentiation and proliferative potential of neural stem cells and progenitor cells.

HD transgenic mouse models have shed further light on SVZ neurogenesis. The most commonly studied transgenic mice are the R6/1 and R6/2 mice, which carry exon 1 of the human *HD* gene, with 115 and 150 CAG repeats, respectively. In human HD, CAG repeat lengths in this range lead to severe symptomatology and death in early infancy; the most common HD CAG repeat range is 40–55 repeats, and this usually results in a disease onset at 40 years of age or more. Of particular interest from the transgenic mouse studies is the finding that R6/2 mice that were housed in an enriched environment (with objects of novelty in the home cage that the mice could explore and play with) demonstrated a delayed onset of HD-like symptoms compared with those that were housed normally[28,33]. Environmental enrichment led to improved motor ability, grip-strength and rota-rod performance. These mice also took longer to develop the genotype-characteristic seizures and had reduced brain-volume loss in the peristriatal region compared with normally housed controls, indicating a delay in the progression of HD symptoms. However, neither of these studies examined the SVZ specifically, nor the effect that enrichment had on the germinal zones[28,33]. Other studies on the R6/1 mice showed a reduction in cell proliferation and neurogenesis in the hippocampus, and no significant change in the SVZ compared with wild-type controls, but the hippocampal reduction was, at least in part, ameliorated by environmental enrichment[34,35]. By contrast, when Batista and colleagues isolated stem cells from the SVZ and formed neurosphere cultures, they found increased neurosphere production in the SVZ of R6/2 HD mice compared with wild-type mice, suggesting that there were more stem cells to begin with[36] (because the number of neurospheres that form from a given number of SVZ cells and their differentiation profile reflect neurogenic potential). Using the neurosphere assay as a measure of neurogenic potential, these results are not in keeping with those of Lazic and colleagues[34–38]. It is possible that generalized cell death in the caudate nucleus is a requirement for the upregulation of SVZ progenitors in HD. This would explain why alterations in the SVZ of the transgenic mice are difficult to detect. In humans, the progressive and massive striatal cell death that occurs in HD causes the SVZ to become significantly thicker (it undergoes a 2.8-fold increase, mostly in layer 3). The cellular composition of the SVZ is also altered, and the number of proliferating type A, B and C cells is increased (there is a 2.6-fold increase overall)[17,39]. In HD brains, the greatest number of proliferating cells is found in layer 3 of the SVZ. Of particular interest is the fact that, despite an approximate 50% increase in the number of type A and C cells, the largest increase is in the number of type B (glial) cells: the ratio of type A:B:C shifts from 1:3:1 in the normal brain to 1:7.5:1 in an HD grade 3 brain[17,18] (FIG. 1c,d).

Several studies have revealed that the SVZ of HD patients is enriched in endogenous factors and receptors that actively regulate the cell cycle and/or the differentiation of precursors. The SVZ of HD patients is enriched in neuropeptide Y (NPY)-positive cells[17] (FIG. 1d). In rodents, NPY powerfully promotes the production of progenitor cells, as evidenced by a 50% reduction in progenitor cells in NPY-knockout mice[40]. In the human brain, NPY-positive cells also express other transmitters, such as nitric oxide synthase (NOS), which in rodents influences progenitor cell proliferation, migration and neurite outgrowth[41,42]. Furthermore, the $GABA_A$ receptor subunit γ2 (involved in the desensitization of the receptor complex to GABA (γ-aminobutyric acid) in the developing SVZ in rodents), which is more enriched in the SVZ than in other regions of the normal brain, is significantly increased in HD[17,43,44] (FIG. 1d). GABA is an important trophic factor for neurons during development[43,44], and the high levels of GABA that are found in the normal SVZ and the SVZ of HD patients suggest that the SVZ maintains a germinal capacity for proliferation and neurogenesis in response to neurodegenerative cell death in adult life.

One criticism of a potential progenitor cell replacement therapy for HD has been the suggestion that endogenous progenitor cells in the SVZ might be prone to the same pathological neurodegenerative processes that affect the cells in the striatum. However, two lines of evidence do not support this. First, in HD, the earliest

Box 2 | **Stroke injury and the subventricular zone (SVZ)**

Stroke, caused by blockage of a cerebral artery, leads to ischaemia and cell death in the brain, resulting in the impairment of sensory, motor and/or cognitive functions. Although the acute treatment has improved dramatically for stroke, the sub-acute treatment modalities remain limited. Experimentally, global and focal ischaemia activate neural progenitor cell proliferation in both the dentate gyrus and the SVZ[129].

After an experimental stroke in the striatum, neural progenitor cells migrate and generate new striatal neurons in the damaged area[7]. Other studies indicate that new neurons can be generated in the cerebral cortex after cerebral ischaemia in the human brain[10,130,131]. Animal models of stroke show that ischaemia-induced neurogenesis can be greatly facilitated by treatment with growth factors (for example, insulin-like growth factor-I (IGF-I) and granulocyte colony-stimulating factor (G-CSF)[132–134]), which markedly improve functional outcome. Recently, stroke-lesioned rats that were housed in an enriched environment (with swings, blocks, textured objects, and so on) were found to have increased numbers of progenitor cells in their SVZs. When these rats were housed in an enriched environment for either 24 hours or 7 days post-stroke and 5 weeks after middle cerebral artery occlusion (MCAO), both groups of animals had similarly higher numbers of progenitor cells in their SVZs than normally caged lesioned controls. These results indicate that environmental enrichment not only increases the number of progenitors in the SVZ, but that it also lengthens progenitor survival in the SVZ[80]. In summary, SVZ progenitor cells and their progeny are likely to have important roles in future stroke therapies that are based on neurogenesis.

sign of neuropathology is a loss of cannabinoid receptors from striatal medium spiny neurons, whereas, even in very late stages of HD, cannabinoid receptors are abundantly expressed on proliferating cell nuclear antigen (PCNA)-positive proliferating progenitor cells in the SVZ[45]. Although it is not clear whether cells that migrate towards the striatum and differentiate would also loose their CB1 receptors, it is likely that the new replacement cells would have a time advantage, as striatal neurons survive approximately 40 years before they degenerate in HD. Second, cells that undergo proliferation may not be affected by the intra-nuclear inclusions that are a pathological hallmark of degenerating mature neurons in the striatum in HD[46,47]. These reports indicate that because inclusions accumulate in neurons over a long period of time in HD, newly born neurons might have a time advantage because they start out with minimal inclusion formation. Therefore, provided that SVZ progenitor cells could be encouraged to migrate into the affected regions, they would appear to have an advantage over the affected cells in the degenerating regions, and they might be of therapeutic benefit.

***Parkinson's disease.*** PD is a movement disorder that is characterized clinically by bradykinesia, rigidity and a resting tremor. It is brought about by a degeneration of the dopaminergic neurons in the substantia nigra pars compacta (SNpc) — part of the basal ganglia circuitry that projects to the striatum and synapses on GABA-releasing projection neurons in the striatum. In the brain, dopamine signals through receptors D1–D5, and its inhibitory or excitatory effect is determined by the receptor subtype. In the striatum, the D1, D2 and D3 receptors are the most abundant. Denervation of the striatum from the substantia nigra leads to hypo-excitation in the motor cortex and, thus, to a paucity of movement. An indication of the functional role of adult neurogenesis in humans might be gained from pathological conditions such as PD. Progenitor proliferation in the SVZ is reduced in animal models and patients with PD. Reduced olfactory bulb (OB) neurogenesis in rodents results in impaired odour discrimination[48] (anosmia), and this is also a common and early sign of PD in humans.

Dopaminergic innervation and signalling in the SVZ profoundly increases the SVZ's proliferative capacity. When the rat medial forebrain bundle was lesioned in order to denervate the SVZ from the SNpc, a decrease in progenitor proliferation in the SVZ was observed, but a large increase in the number of PAX6-positive dopaminergic interneurons in the periglomerular layer and a decrease in the granule cell layer in the OB occurred. Overall, there was an increase in the number of dopaminergic neurons in the rodent OB[49,50]. Similarly, in PD patients, there is also a marked increase in the number of dopaminergic neurons in the periglomerular layer[51]. Despite the reported diffusion of dopamine up to 15 μm from dopamine-releasing synapses, because the striatum is separated from the SVZ by myelin, it is very unlikely that diffusion

Box 3 | **The hippocampal subgranular zone and epilepsy**

In addition to the subventricular zone (SVZ), the other germinal zone in the adult mammalian brain that contains progenitor cells is the subgranular zone of the hippocampus[13,135]. Here the progenitor cells are involved in memory and learning, and neurogenesis continues throughout the life of the animal[136–140]. Epilepsy is caused by abnormal and disorganized electrico-stimulatory impulses in the hippocampus, and it is modelled in rodents by injecting the hippocampus with kainic acid, with an *N*-methyl-D-aspartate (NMDA) agonist such as pilocarpine, or by kindling the hippocampus or piriform cortex with trains of electrical impulses. In all the epilepsy models that have been examined, an increase in hippocampal neurogenesis has been observed[11,141–146]. This could be due to neurodegeneration (hippocampal cells are lost in these models), but it seems more likely that neurogenesis may actually cause an increase in abnormal circuitry and even propagate epilepsy, as the newly formed neurons are more sensitive to stimulation than older generated neurons[147-149]. Usually neurogenesis occurred in the first 2 weeks following excitotoxin injection in animal models. Some of those neurons generated in the first 2 weeks could survive for up to 6 months. The overall number of mature neurons (NeuN-positive) in the granule cell layer did not change, suggesting that newly generated neurons might replace dead cells[150]. In addition to the neurogenic events that take place in the hippocampus in epilepsy, mossy fibre sprouting also occurs. These new neurons do not project to the CA3 region, but to the granule cell layer and molecular layer instead[148]. Thus, it appears that hippocampal neurogenesis in epilepsy may in fact be a detrimental event. However, in animal models of epilepsy, prolonged seizures lead to increased cell proliferation in the SVZ and recruitment to the hippocampus, where most of the recruited cells have either a neuroblast or glial phenotype[11,145]. Therefore, it may be that the locally derived neurogenesis is harmful but that cells recruited from the SVZ are beneficial.

Differentiation
The process whereby an unspecialized cell develops the specialized functions of a mature cell, for example, a neuron, or a liver or muscle cell.

Acute treatment
A remedial action that is administered within the first few hours of a neurodegenerative or necrotic event such as a stroke.

Sub-acute treatment
A remedial action that is administered after the initial neurodegenerative and/or necrotic events of a stroke are over.

Proliferating cell nuclear antigen
(PCNA). A cell-cycle protein that is expressed during, and shortly after, G1 and S-phase. It is used as a marker of recent cell division.

Substantia nigra pars compacta
(SNpc). The area of the brain where dopamine is produced. It is also one of the basal ganglia nuclei.

Box 4 | **Why don't animal data always reflect observations in the human brain?**

The three main reasons why rodent models of neurodegeneration don't always give the same results that are seen on examination of the human subventricular zone (SVZ) are: the model might not cause neurodegeneration; the model might cause degeneration in a region that is not under the developmental control of the SVZ; or the model might have no effect on the regions that are being examined[34,35]. In addition, rodents are not treated with the same drugs used in humans patients, which might also affect proliferation in the human SVZ. Rodent models of neurodegenerative diseases are developed in an attempt to replicate one or more of the cardinal features of a disorder. For instance, the R6/1 and R6/2 transgenic mouse models of Huntington's disease (HD) have an exaggerated CAG repeat expansion but exhibit limited neurodegeration[151,152], whereas the excitotoxic lesion (pathological) model of HD, in which quinolinic, kainic or ibotenic acid is injected into the striatum[153–156], shows the most advanced pattern of HD neurodegeneration but lacks the HD genotype. In the case of the transgenic models, because the age of a rodent is so short, it is necessary to use an excessive CAG-repeat length in order to see early signs of neurodegeration in the normal lifespan of the animal. It is also worth noting that in transgenic models SVZ alterations are harder to visualize due to the minimal striatal-cell loss. By contrast, in excitotoxic lesion models, it is impossible to see how the defective gene causes nuclear inclusions and other pathological changes, but SVZ changes are readily visualized because of the advanced cell loss. There are also differences in the levels of key transcriptional regulators of neurogenesis between rodent and human SVZ, such as activated transcription factor-2 (ATF-2), which is crucial for neuronal differentiation in the human SVZ but may not be so important in the rodent SVZ[116]. Furthermore, in the SVZ, very acute conditions such as stroke cause very rapid SVZ changes that normalize over time, unless the pathological event happens close to the SVZ[7,12,157,158]. It is always important to appreciate the purpose of the animal model, as few rodent models of neurodegeneration replicate all the cardinal features of the disease that is under study.

of dopamine from the striatum would affect the SVZ. However, in mice the dopaminergic innervation overlaps the entire rostrocaudal extent of the SVZ, as evidenced by tyrosine hydroxylase staining[52]. In particular, the D2 receptor seems to have a vital role in upregulating the proliferation of progenitor cells in the SVZ. A recent study used a 6-hydroxydopamine (6-OHDA) lesion model of PD, in which the medial forebrain bundle (also known as the nigrostriatal pathway) is destroyed by an excitotoxin, and measured proliferation in the SVZ. The number of proliferating cells was found to have decreased by approximately 40%, as measured by bromodeoxyuridine (BrdU)-positive cell counts. Furthermore, this study demonstrated that the amount of proliferation in the SVZ after a 6-OHDA lesion was proportional to the amount of remaining dopaminergic innervation in the striatum. After the dopamine precursor levodopa was administered, normal proliferation levels were restored in the side ipsilateral to the lesion, however, on the contralateral side, levodopa had no effect[49].

In both the embryonic proliferative lining of the neural tube and in the adult SVZ there is an abundance of D3 receptors. Furthermore, stimulation of D2 receptors in the embryo promotes the production of striatal neurons[3]. Agonists of both D2 and D3 receptors have a powerful effect at upregulating proliferation in the rat SVZ[3,53]; however, stimulation of the D3 receptor in mice (in which it is the sole dopamine receptor expressed in the SVZ), does not affect the proliferation potential of the SVZ, suggesting species-specific alterations in the control of SVZ proliferation[54].

In one study, infusion of transforming growth factor-α (TGFα) into the unilateral striatum, together with a 6-OHDA lesion to the substantia nigra ventral tegmental area, led to a wave of SVZ proliferation[55]. Migration was directed to the striatum, and the progenitors differentiated to a dopaminergic neuronal fate. However, in another similar study, after a unilateral lesion to the medial forebrain bundle, intraventricular infusions of TGFα revealed a bilateral wave of progenitor cells migrating rostral to the TGFα injection, but the expanded population of SVZ progenitor cells was primarily PCNA- and nestin (a progenitor cell marker)-positive and exhibited a glial morphology rather than a dopaminergic fate[56]. In contrast to the study by Fallon and colleagues, Hoglinger and colleagues showed that, after BrdU injection, most of the BrdU-stained cells in the SVZ were in close proximity to dopaminergic fibres that projected from the substantia nigra, and were in fact type B cells that produce type C cells (transit amplifying cells); these, in turn, give rise to type A cells that migrate to the olfactory bulb[56] (FIG. 1e). The ultrastructure of the SVZ revealed that type B cells usually separated type A cells from the dopaminergic fibres, whereas type C cells were in direct contact with them. Synaptophysin was also present on the type C cells, indicating that these cells might be involved in exocytosis and thus might engage in active neurotransmission[49,52] (FIG. 1e). Because the type A cells are generated by type C cells, there is also a reduction in the number of type A cells that migrate to the olfactory bulb after dopaminergic denervation in the striatum[49]. These findings suggest that in the absence of dopamine, TGFα can partially restore the proliferation of neuroblasts in the SVZ and induce their migration towards the injury site. However, as these results demonstrate a gliogenic fate, the use of another mitogenic factor would be necessary to induce a dopaminergic fate in the progenitor cells after migration.

In the human brain, type B cells also separate type A cells from the dopaminergic nerve terminals. The PD models appear to reflect the human condition because, based on cell counts of PCNA-positive cells in the SVZ of clinically diagnosed patients with PD, there is a decrease in SVZ cell proliferation of approximately 30%. There is also a significant reduction in the number of β-III tubulin (an immature neuron marker that is downregulated as the neuron matures)-positive cells and a 40% reduction nestin-positive cells in the dentate gyrus[49].

Levodopa
The most commonly used drug for the treatment of Parkinson's disease. After administration, it is converted into dopamine, such that it raises the levels of dopamine in the brain. Levodopa treatment is an effective control of Parkinson's disease symptoms, however, its long-term use is associated with complications.

Transit-amplifying cell
A type of proliferative stem cell that is able to divide only 3–5 times before all of its daughter cells terminally differentiate.

***Alzheimer´s disease.*** AD is a neurodegenerative disorder that is characterized by the accumulation of neurofibrillary tangles and amyloid plaques. The major constituent of amyloid deposits are the β-amyloid (Aβ) peptides, which are derived from the amyloid precursor protein (APP). Neurofibrillary tangles are made up of paired filaments and comprise abnormally phosphorylated forms of the microtubule-associated protein tau[57].

In AD, Aβ promotes synaptic dysfunction and causes the death of mature neurons[58]. Newly formed hippocampal neurons are sensitive to the intensity of synaptic transmission, but it is unclear what happens in the SVZ[59]. How Aβ or Aβ fibrils interfere with the synaptic function remains unknown, but this process is likely to be important for understanding the pathological effects of Aβ on adult neurogenesis[60].

A limited number of studies have focused on changes in the expression of immature neuronal markers in the hippocampus and SVZ of patients with AD. One report showed an increase in neuroblast markers in a cohort of senile AD cases, suggesting that neurogenesis could be increased in the hippocampus in AD[61]. However, these results could not be replicated in a younger cohort of pre-senile patients with a more aggressive form of the disease[62]. Although the number of cells that express the cell cycle marker Ki-67 was significantly increased, a detailed analysis revealed that this was largely due to the generation of mostly non-neuronal cells. Furthermore, animal studies that used other AD models that were based on presenilin 1 (PSEN1) transgenes or intraventricular infusion of Aβ reported an impairment of adult neurogenesis[63–67].

Human studies are inherently complicated, because of factors such as the stage of the disease, post mortem delay, the effects of medication, and other inter-individual differences. However, several studies have now consistently shown a connection between AD and a decrease in neurogenesis. Patients with mild cognitive impairment and olfactory identification deficits, particularly those that have a lack of awareness of these deficits, are more likely to develop AD than other patients[68], and there is some evidence that the severity of the olfactory dysfunction increases with the severity of dementia[69–71]. These results indicate that AD is associated with a disruption of olfactory neurogenesis.

Aβ impairs the proliferation and neuronal differentiation of cultured human and rodent neural progenitor cells, and it also promotes apoptosis in neuron-restricted neural progenitor cells[64,65]. In addition, the proliferation and migration of neural progenitor cells in the SVZ was markedly reduced in mice that were injected with Aβ into their lateral ventricles[65] (FIG. 1f). A ninefold decrease in the number of musashi 1 (a neural precursor marker)-immunoreactive progenitor cells in the SVZ of patients with AD has been reported[72]. Interestingly, ependymal cells and a subpopulation of subependymal astroglial cells in the SVZ show APP-like immunoreactivity. Furthermore, APP-like immunoreactivity was found in 'glial tubes' — bundles of glial cells through which progenitor cells migrate in the RMS. Double-immunofluorescent labelling with a highly polysialylated neural cell adhesion molecule (PSA-NCAM) confirmed that the APP-like immunoreactive astrocytes in the SVZ and the RMS made close contact with PSA-NCAM-immunopositive neuroblasts, suggesting an interaction between APP-containing cells and neuroblasts[73] (FIG. 1f).

APP is a type I transmembrane protein of unknown physiological function, but its soluble secreted form (sAPP) shows similarities with growth factors and increases the *in vitro* proliferation of embryonic neural stem cells[74]. sAPP binds to SVZ progenitor cells that express the epidermal growth factor (EGF) receptor and increases their proliferation *in vivo*[75]. Conversely, blocking sAPP secretion or downregulating APP synthesis decreases the proliferation of EGF-responsive cells and leads to a reduction of the pool of progenitors, suggesting another function for sAPP as a regulator of SVZ progenitor proliferation in the adult CNS[76]. The balance between the generation of non-amyloidogenic peptides (which are generated through cleavage of APP by α-secretase) versus amyloidogenic peptides (which are generated through cleavage of APP by β-secretase) may have a pivotal role also for adult neurogenesis in the ventriculo-olfactory neurogenic system (VONS).

ADAM10, a member of the A disintegrin and metalloproteinase (ADAM) family, is one of the α-secretases that leads to increased amounts of sAPP and, thereby, to decreased formation of the toxic Aβ protein, but it is expressed in limited amounts in the adult rat or mouse SVZ[77]. Interestingly, ADAM21-like immunoreactivity (ADAM21 is another probable α-secretase) is present in significant amounts in the ventricular ependyma and in radial glia-like cells that are intermingled with the neural precursors and astrocytes of the postnatal and adult SVZ[77]. The functions of ADAM21 in the SVZ remain to be determined. These findings suggest that increasing the expression of ADAMs by using local gene therapy or pharmacological induction might promote the production of non-amyloidogenic peptides, decrease the generation of amyloidogenic peptides and restore neurogenesis in AD.

Using a different strategy, Becker and colleagues recently showed that immunotherapy against the N-terminus of Aβ stimulates endogenous neurogenesis[78]. They found that a high number of cells had incorporated BrdU and co-localized with a marker of mature neurons, suggesting that anti-amyloid immunotherapy may promote recovery from Aβ-peptide overproduction and neurotoxicity by partially restoring the neuronal population and potentially restoring cognitive functions[78].

In mice, living in an enriched environment has also been shown to induce brain plasticity and neurogenesis[79–81]. Interestingly, exposing a transgenic mouse model of AD to an enriched environment resulted in pronounced reductions in cerebral Aβ levels and amyloid deposits, compared with animals raised under standard housing conditions[82]. The enzymatic activity of an Aβ-degrading endopeptidase, neprilysin, is elevated in the brains of 'enriched' mice and inversely correlated with the amyloid burden. Furthermore, DNA microarray analysis revealed selective upregulation of transcripts encoded by genes that are associated with

β-amyloid (Aβ) peptide
A peptide that is derived from amyloid precursor protein. These peptides are the main protein component of amyloid plaques.

Amyloid precursor protein
(APP). A membrane glycoprotein component of fast axonal transport that is cleaved by secretases to give rise to Aβ.

Neural stem cell
A stem cell that is found in adult neural tissue and can give rise to neurons and glial cells.

Radial glial cell
A connective tissue cell that guides the migration of neurons from the SVZ to the cortex. Radial glia are also a major source of cortical neurons during development.

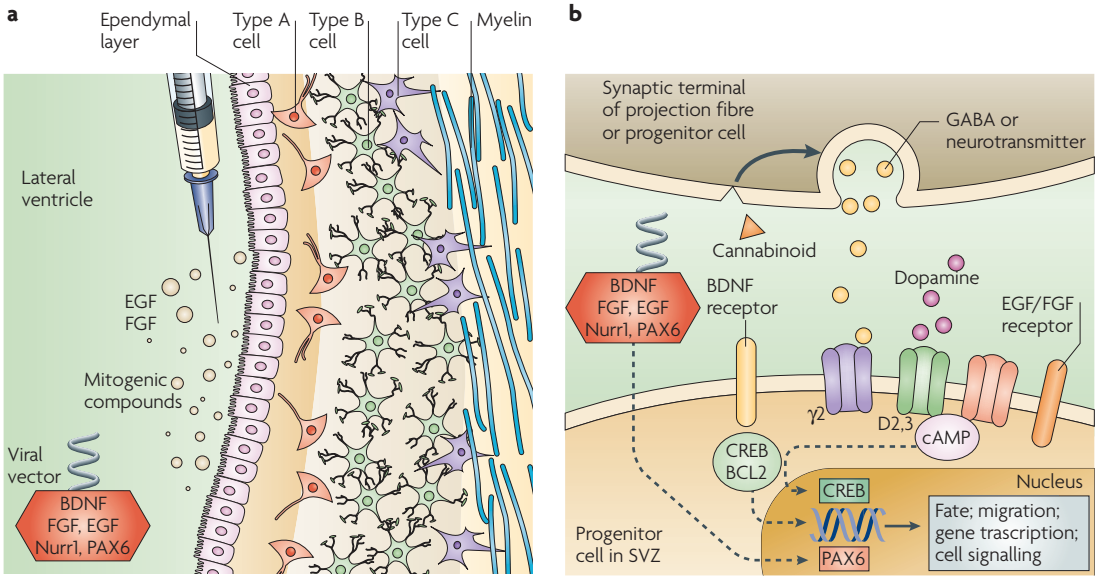



Figure 2 | **Representations of possible therapeutic interventions in the subventricular zone (SVZ) for neurodegenerative diseases. a** | The insertion of a needle into the lateral ventricle is one possible method for delivering a viral vector, mitogenic compounds, transcription factors or other progenitor-cell-enhancing agents. **b** | Growth factors, such as epidermal growth factor (EGF), fibroblast growth factor (FGF), brain derived neurotrophic factor (BDNF), Nurr1 or PAX6, may be administered to SVZ progenitor cells directly through the lateral ventricle, or indirectly, in the form of a viral vector. By infecting SVZ cells, viral vectors could potentially bring about prolonged and possibly controllable effects on progenitor cells. It may also be possible to affect SVZ progenitor cells by administering compounds that work on the cannabinoid or other systems. These potential therapies have been tested in rodents. Cyclic adenosine monophosphate (cAMP) is affected after stimulation of the metabotropic receptor on the cell surface and B-cell lymphoma protein 2 (BCL2) is involved in anti-apoptotic mechanisms, allowing more progenitors to remain alive; neurotransmitters affect the signalling, and therefore the input, to progenitor cells. CREB, cyclic AMP response element binding protein; GABA, γ-aminobutyric acid.

learning and memory, vasculogenesis, neurogenesis, cell survival pathways, Aβ sequestration and prostaglandin synthesis[82]. These studies provide further evidence of a decrease in neurogenesis in AD.

## Therapeutic manipulation of the SVZ cells

The pathologies of HD, AD and PD are evidenced by a loss of neurons in specific brain regions. In the case of HD, the SVZ responds to the nearby striatal degeneration by upregulating the production of progenitor cells. In AD there is cholinergic cell loss in the cortex, and Aβ protein is toxic to the SVZ progenitor cells. In PD there is also a decrease in progenitor cell proliferation, due to dopaminergic denervation of the SVZ progenitors by the substantia nigra. In each of these cases, if the rate of progenitor proliferation and subsequent migration could be improved therapeutically, then symptomatic improvements as a result of cell replacement in the diseased area might be possible. These therapies could use one or a combination of the following techniques: drug therapy using endogenous compounds; progenitor cell transplantation to remove, culture and replant the expanded cells into the disease affected region; transcription factor (TF) manipulation to alter the fate of the SVZ progenitor cells; or viral implantation to allow a growth factor to be widely spread across many progenitor cells. Each of these techniques is discussed below.

***Drug therapy.*** Neural progenitor cells in the SVZ respond to a variety of endogenous mitogenic and trophic growth factors that affect cell proliferation, migration and maturation. EGF[83–86], fibroblast growth factor 2 (FGF2)[85,87], brain-derived growth factor (BDNF)[88,89], nerve growth factor (NGF), insulin-like growth factor 1 (IGF1) and erythropoietin (EPO) all stimulate the production of progenitor cells in the SVZ (FIG. 2). These factors are endogenous to the brain, however, exogenous factors can also influence proliferation in the progenitor cell pool. For example, pharmacological compounds such as lithium and fluoxetine (both of which are antidepressant drugs that are commonly prescribed for the treatment of recurrent mood disorders) increase the number of proliferating cells in the brain[90,91]. In particular, mice that had been chronically administered lithium and the cell cycle marker BrdU demonstrated a 25% increase in the number of proliferating cells in the dentate gyrus of the hippocampus[92,93]. This effect was due to an increase in the levels of B-cell lymphoma protein 2 (BCL2), which exerts a major anti-apoptotic and neuroprotective effect both *in vitro* and *in vivo,* and probably exerts a trophic effect as well[92,94–96]. If these compounds could be given either orally or by intraventricular injection, it is conceivable that the effect of increasing the proliferation of the progenitor pool may lead to more widespread cell replacement strategies in human neurodegenerative diseases. Although the administration of these antidepressants

may not prove successful, it is important to note that some of them are already given to treat other disorders that may or may not be related to disorders of proliferation.

One system that may prove effective as a drug target is the cannabinoid system: knocking out the cannabinoid receptor in mice leads to a 50% reduction in progenitor cell proliferation[61]. This cannabinoid treatment may well prove useful in HD, as the main sign of HD pathology is the loss of CB1 receptors from striatopallidal projection neurons. However, cannabinoid receptors are not lost in the SVZ in HD, and neither are the cells that express compounds such as NPY, indicating that they may be a useful source of cells for cell replacement therapies for diseases like HD as they are not affected by the pathological process. These compounds could be delivered by intraventricular injection to stimulate a neuronal replacement response, perhaps in combination with TGFα to enhance subsequent cell migration (FIG. 2).

***Progenitor cell transplantation.*** Presently, we do not yet know enough about the factors that are required to manipulate the direction and fate, or the number of, dividing cells in the SVZ. This has lead to the development of transplantation strategies whereby SVZ progenitor cells are removed and cultured into neurospheres, and then, with sufficient cell confluence and suitable differentiation cues, transplanted back into the region of neurodegeneration in the donor[97–100]. In rodent studies in which exogenous progenitor cells have been labelled before being transplanted into the disease-affected region, the transplanted cells appear to have similar electrophysiological properties to non-transplanted cells in the brain tissue near to the transplant[101]. Some studies even demonstrated functional improvement after the transplants. In fact, when SVZ explant cultures are labelled and transplanted back into the SVZ, they migrate to the olfactory bulb just as normal SVZ progenitors would[100,102]. In one such study, Shim and colleagues used a retrovirus to overexpress the TF Nurr1, which specifies progenitors to adopt a dopaminergic fate. After expansion of the dopaminergic cell population, the cells were transplanted back into the dopamine-depleted striatum of parkinsonian rats, resulting in an improvement in the animals' behaviour[103]. However, transplant studies in disease-affected brains have yet to show better results than studies that used embryonic tissue as the source of progenitor cells[104]. Embryonic studies involve removing fetal or embryonic brain tissue and subsequently transplanting it into the region of degeneration. Embryonic transplants have been trialled in rodents and humans and have attained relatively good success, however, in human trials they have not been considered successful enough to be offered as a routine treatment for neurodegenerative disorders such as PD or HD[1,101,105–109]. The two major problems with this technique are the ethical issues of obtaining the embryonic tissue, and graft rejection. These problems could be overcome by performing a transplant of progenitor cells that are expanded from the patient's own SVZ. To date, no human autologous transplant studies have been reported in the scientific literature.

Autologous transplant
A tissue transplant in which a patient's own progenitor cells are removed, expanded in culture and then transplanted back into the disease-affected region.

***Transcription-factor therapy and cell-fate manipulation.*** The principle of a TF-based therapy for the treatment of neurodegenerative diseases is to drive SVZ progenitors to become the cell type that is affected by the disease, by either administering the TFs directly or by making the progenitors express TFs that specify a particular neuronal fate (FIG. 2). For example, in the SVZ, the TF Meis2 causes progenitor cells to adopt a striatal neuron phenotype, and after middle cerebral artery occlusion (MCAO) in a mouse stroke model (see BOX 2), most of the cells that migrate into the striatum are positive for Meis2, and go on to become functional striatal neurons[7]. If the fate of progenitors in the SVZ could be altered by the induction of Meis2, then more striatal neurons might be replaced in HD.

In the SVZ, the TF SOX2 specifies progenitors to a glial fate, or acts to counter neuronal differentiation by interacting with pro-neural basic helix-loop-helix factors[110–112]. Conversely, PAX6, an important regulator of brain patterning during development, retains its ability in the adult to differentiate SVZ progenitors to a neuronal fate *in vivo*, and in the OB it is responsible for the generation of dopaminergic neurons[113,114]. Interestingly, in the human brain PAX6 is expressed in PSA-NCAM-positive progenitors that would normally be destined either for the striatum or for the olfactory bulb[112–114]. The ability of PAX6 to specify a dopaminergic phenotype could be used therapeutically; for instance, PAX6 overexpression in the SVZ might induce more progenitor cells to migrate from the SVZ towards diseased areas of the brain (such as to the striatum or the substantia nigra in PD).

Knockout mouse studies have also demonstrated that the presence of activating transcription factor 2 (ATF2) is required for correct neurological development and neuronal migration[115]. Therefore, ATF2 is another TF that could be manipulated to potentially induce the generation of mature neuronal populations from progenitors near the striatum in HD[115]. ATF2 co-localizes with PCNA, as well as with both the glial marker GFAP and the neuronal microtubule marker MAP2, indicating that ATF2 may have a role in promoting SVZ progenitor cell survival and differentiation[116].

From a therapeutic perspective, for endogenous progenitor cell therapy to become a reality, an in-depth knowledge of the TF expression requirement for specific cell types in the SVZ will be paramount. Experimentation on possible therapeutic delivery strategies, such as retroviral implantation, also needs to be undertaken.

***Viral implantation.*** The use of *in vivo* gene transfer techniques may provide an alternative technique for delivering mitogenic factors to progenitor cells in the SVZ of the adult brain. Intraventricular delivery of a viral vector (such as adenovirus, adeno-associated virus, herpes simplex virus or retrovirus) encoding a mitogenic factor such as FGF2, BDNF or a TF would allow direct targeting of the cells of interest in the SVZ (FIG. 2). The advantages of such a system are that it would allow the sustained expression of exogenous mitogens in neurogenic regions, and that there would be no

adverse effects due to peripheral administration. To date, several studies have demonstrated that viral delivery of mitogenic factors such as BDNF[89] or FGF2[117,118] by gene transfer can result in proliferation in the SVZ and recruitment to damaged areas of the brain[119–122]. However, viral implantation is also useful for getting TFs into cells and altering their fate[103,123]. One advantage of using a viral gene transfer method is that it is possible to regulate the production of the mitogen or TF by using, for example, a tetracycline-regulated system, leading to greater control over the expression of the mitogen or TF and, therefore, providing a means to vary the levels according to the patient's symptom response.

## Conclusions and future directions

Although the potential usefulness of neurogenesis in the adult human SVZ remains to be fully demonstrated, it is clear that after a neurodegenerative or necrotic event such as HD or stroke, there is an upregulation of progenitor cell proliferation. It is difficult to definitively conclude whether or not there is an increase in proliferation in AD, as the effect could be masked by the Aβ toxicity that surrounds the progenitor cells. In the case of PD, the signal for progenitor cell proliferation is dramatically reduced as the dopaminergic signal is depleted, owing to the neurodegeneration of the nigrostriatal pathway. Interestingly, the closer the neurodegenerative event is to the SVZ, the more likely it is that upregulation of the SVZ progenitors occurs (as is the case in HD). Furthermore, in all of the neurodegenerative disorders that are reviewed here, replacement of the dying neurons would be beneficial if the replacement could take place in an efficient, region-specific and non-tumorigenic way. It would also be extremely beneficial to develop better methods for detecting the progenitor cells that are born in and migrate from the SVZ. To date, the best method of labelling progenitor cells is by using BrdU, which is impractical for most studies that involve human brains. Moreover, the long-term survival of newly generated neurons could be monitored if a better progenitor cell labelling system were developed.

Although there is evidence that in epilepsy local hippocampal neurogenesis may be detrimental (see BOX 3), there is no such evidence from studies of the SVZ progenitors in animal models of AD, HD and PD. Therefore, if the progenitor cells in the SVZ could be enhanced so that they survive and integrate despite the surrounding pathological events, then the effect of the pathology could be slowed, halted or even reversed. Future research must investigate the transcriptional regulation of progenitor cells in the SVZ so that the key fate specification factors can be determined. When the fate of the progenitor cells can be directed, it will be possible to replace the disease-affected cells with the correct phenotype in the appropriate brain region (for example, substantia nigra in PD). It is also essential that we study progenitor cell migration in the brain, so that progenitor cells can be made to migrate to the correct site of disease. Progenitor cell migration in the mammalian brain has only recently been explored, and there is much to learn about post-developmental migration in terms of chemoattraction to the site of injury and disengagement of the migrational machinery when the cells arrive at the injury site. By enhancing SVZ progenitor cell proliferation and migration towards the site of injury, as well as the successful integration of the progenitors into the damaged tissue, future research may improve longevity and quality of life for sufferers of neurodegenerative diseases.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**Review of stroke and epilepsy studies on proliferation in the germinal zones in rodent brains.**

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## Competing interest statement
The authors declare no competing financial interests.

## DATABASES
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